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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,386	12/27/2004	Marie-Noelle Horcajada	P70350US0	6940

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EXAMINER	
JAVANMARD, SAHAR	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,386	HORCAJADA ET AL.	
	Examiner	Art Unit	
	SAHAR JAVANMARD	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-11 and 13-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-11 and 13-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to applicant's arguments filed on 1/07/2008. Claim(s) 2-11 and 13-22 are pending. Claim(s) 1-5 have been amended. Claim(s) 2-11 and 13-22 are examined herein.

Response to Arguments

In view of applicants amendments the 35 USC 101 rejection of claims 1-11 and 13-20 is herein withdrawn.

Applicant's arguments with respect to the 112 1st rejection as it applies claims 4, 5, 7, 15, 16, and 18 over the term "prevention" was not found persuasive.

Applicant's arguments that there are working examples in the specification and the Shen reference are not persuasive. Examiner has considered examples 1 and 3 in the specification and notes that although prevention of bone loss may be observed following estrogen deficiency in the oophorectonized rats after a period of three months, there is no evidence that this prevention will continue totally, absolutely, or permanently. Similarly, the Shen reference does not demonstrate total, absolute, or permanent prevention.

The Applicant argues that, "the claims do not recite or require total prevention, but rather induction of a preventative effect that would at least postpone or reduce the occurrence of the bone disorder. Examiner respectfully notes that the limitations of the claims are not as such.

Furthermore, in regard to Applicant's comment on previous U.S. patents that have been granted which cite "prevention", Examiner respectfully notes that each case is treated on its own merit. Thus the 112 1st rejection is hereby maintained and is restated below for Applicant's convenience.

Applicant's arguments with respect to the 112 2nd rejection of claims 1-11 and 13-20 as it applies to the term "derivative" and the recitation of "use" claims has been considered and in view of Applicant's amendments, the rejection is hereby withdrawn.

Applicant's cancellation of claims 1 and 12 have rendered the 102(b) rejection moot, therefore hereby withdrawn.

Applicant's arguments with respect to claims 2-9 11, and 13-20 to the 102(b) rejection of Wenzel have been fully considered but not found persuasive. It is well known in the art that inhibition of COX-2 and NF-kB activity can be employed in the treatment of osteoporosis and other bone related diseases, therefore Wenzel anticipates the instant claims.

Applicant's arguments with respect to claims 2-7 and 13-19 to the 102(b) rejection of Kise have been fully considered but not found persuasive. Applicant argues that the hesperidin present in the composition is used as a stabilizer for the unstable vitamin K (see Applicant's arguments 01/07/08). Examiner notes that "products of identical chemical composition can not have mutual exclusive properties." Any properties exhibited by or benefits from are not given any patentable weight over the prior art provided the composition is inherent. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the

disclosed properties are necessarily present. In re *Spada*, 911 F.2d 705,709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The burden is shifted to the applicant to show that the prior art product does not inherently possess the same properties as the instantly claimed product.

Applicant's arguments with respect to claim 9 to the 103(a) rejection of Wenzel in view of Barnes have been fully considered but not found persuasive. Although genistein is an isoflavone and hesperidin is a flavone, both are used to treat bone related disorders (i.e., osteoporosis) in foodstuffs, therefore it would be obvious to one of ordinary skill in the art to apply this method for the treatment of animals as well. Thus the 103(a) rejection is maintained. In view of applicants amendments the following modified 35 USC 112-1, 102(b) and 103(a) rejections are being made.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 5, 7, 15, 16, and 18 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the treatment of disorders linked to an imbalance in the relationship between bone formation and bone resorption including a disease selected from osteoporosis, Paget's disease, bone loss or the osteolysis observed close to a prosthesis, metastatic bone diseases, the hypercalcemia due to a cancer, multiple myelomas, periodontal diseases

or osteoarthritis disclosed in the specification, does not reasonably provide enablement for the prevention of the imbalance in the relationship between bone formation and bone resorption of the disorders recited in these claims.

The instant claims are drawn to a composition for the prevention of one or more symptoms of diseases or disorders associated with the imbalance in the relationship between bone formation and bone resorption of the disorders. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The instant invention pertains to a composition for the prevention of one or more symptoms of diseases or disorders associated with the imbalance in the relationship between bone formation and bone resorption of the disorders.

The state of the prior art:

One of ordinary skill in the art would appreciate that the prevention of one or more symptoms of diseases or disorders associated with the imbalance in the relationship between bone formation and bone resorption totally, absolutely, or permanently, is highly unlikely, since it is impossible to totally prevent disorders linked to an imbalance in the relationship between bone formation and bone resorption.

The relative skill of those in the art:

The relative skill of those in the art is very high.

The predictability or lack thereof in the art:

The ordinary artisan would view that the prevention of one or more symptoms of diseases or disorders associated with the imbalance in the relationship between bone formation and bone resorption, absolutely, or permanently is highly unpredictable, and since no one can guarantee that the diseases will be totally prevented.

The amount of direction or guidance presented and the presence or absence of working examples:

In the instant case, no working examples are presented in the specification as filed showing how to prevent one or more symptoms of diseases or disorders associated with the imbalance in the relationship between bone formation and bone resorption totally, absolutely, or permanently. Note that the lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and

undeveloped art. See MPEP 2164.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, e.g., the amount of direction or guidance provided, absence of working examples, and the predictability of the art discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test the combination in the instant claims whether preventing one or more symptoms of diseases or disorders associated with the imbalance in the relationship between bone formation and bone resorption totally, absolutely, or permanently, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 2-9, 11, 13-20 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Wenzel et al. (EP 1127572A2).

Wenzel teaches compositions of flavone-type compounds of formula I, specifically hesperidin and hesperitin (Table 3) are useful in the treatment of cyclooxygenase-2 (COX-2) and nuclear factor kappa B (NF-kB) mediated diseases (page 2, lines 23-24).

COX-2 mediated diseases encompass acute exuditive inflammation, proliferative inflammation, animal arthritis, rheumatoid arthritis, angiogenesis, bone absorption, gastric ulcer, colon cancer, hyperalgesia, Alzheimer's disease, and certain states of the kidney, brain, and female reproductive organs (Katori, et al., Inflamm. Res., 49, 2000, p 367-392, abstract).

NF-kB mediated diseases include postmenopausal osteoporosis, rheumatoid arthritis, Paget's disease, periodontal disease, benign and malignant bone tumors, bone metastases, and hypercalcemia of malignancy (Hofbauer et al, J. Mol. Med., 79, 2001, p 243-253, abstract).

Thus the limitations of claim 21 are met.

In addition, Wenzel teaches, compositions of the compounds of formula I may be used as dietary supplements, added as the active ingredient to foods or medical foods or as oral compositions to treat COX-2 and NF-kB mediated diseases (page 8, lines 33-37; page 11, example 1; page 12, examples 5 and 6), meeting the limitations of claims 2.

Further, by definition, bone is hard tissue that is in a constant state of flux, being built up by bone-forming cells called osteoblasts while also being broken down or

resorbed by cells known as osteoclasts. Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures, especially of the hip, spine, and wrist. Osteoporosis occurs primarily as a result of normal ageing, but can arise as a result of impaired development of peak bone mass (e.g. due to delayed puberty or undernutrition) or excessive bone loss during adulthood (e.g. due to estrogen deficiency in women, undernutrition, or corticosteroid use) (defined by the World Health Organization). Thus the limitations of claims 4, 5, 6, and 7 are also met.

The reference teaches the compounds of formula I can be added to nutritional substances which can be a food preparation or an essential nutrient preparation. Food preparations particularly well suited include breakfast foods, such as prepared cereals, toaster pastries, and breakfast drink mixes; infant formulas; dietary supplements; complete diet formulas; and weight-loss preparations, such as weight-loss drinks and weight-loss bars (page 10, lines 50-52; page 11, example 1; page 12, example 6), meeting the limitations of claims 3 and 8.

Furthermore, in example 6, an infant formula containing the flavone is administered, thus meeting a drink in wet form, meeting the limitations of claim 9.

Wenzel teaches the daily quantity of compounds of formula I by oral administration is between 10 mg to 700 mg (page 11 and 12, examples), meeting the limitations of claim 11.

Wenzel teaches the pharmaceutical compositions of formula I for the treatment of COX-2 and NF-kB mediated diseases to humans and other animals administered orally,

rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, or as an oral or nasal spray (page 8, lines 1-4), meeting the limitations of claims 13-19.

Further, Wenzel teaches that the total daily dose of the compounds of formula I administered to a human in single or in divided doses can be in amounts, for example, from 0.05 to about 500 mg/kg body weight daily or more preferably from about 1 to about 150 mg/kg body weight for oral administration or 0.01 to about 10 mg/kg for parenteral administration daily (page 12, lines 37-40), meeting the limitations of claim 20.

Claims 2-7, 9-10, 13-19, and 21-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Kise et al. (JP 2001114675A, enclosed is a machine translation that is being relied upon).

Kise teaches a vitamin composition containing vitamin K and flavonoids, including hesperidin or hesperitin (claims 1 and 3). Further, the reference teaches that the hesperidin is an extract of the fruit juice of citrus fruits (claim 7). The reference further teaches that compositions of vitamin K, vitamin D3, estrogen, isoflavone, etc., are known to prevent and treat osteoporosis (page 2, [0003]). Kise also teaches that the composition can be in a soft capsule (page 5, [022]), meeting the limitations of claims 2-7, 9-10, 12-19, and 21-22.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wenzel et al. (EP 1127572A2) as applied to claims 2-9, 11, 13-20, and 22 above in view of Barnes et al. (US Patent No. 5,506,211).

Wenzel is discussed above.

Wenzel does not teach the nutritional composition of hesperidin or one of its derivatives in the form of animal feed in a wet, semi-wet, or dry form.

Barnes teaches genistein, which is used to provide a method of use in inhibiting osteoclast activity to reduce bone loss (ie, in patients with osteoporosis), may be present in a variety of foodstuffs, particularly soy products, and may be ingested by animals to provide them with an effective amount genistein (column 3, lines 5-10).

Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to have combined the methods of use of hesperidin as taught by Wenzel and used it in foodstuffs to be ingested by animals as taught by Barnes. Humans and animals can suffer from the same ailments; therefore, one would be motivated to use the same methods of treatment in animals as in humans.

Conclusion

Claims 2-11 and 13-22 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/S. J./

Examiner, Art Unit 1617

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617